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A Public Health Approach to the Prevention of Inhibitors in Hemophilia

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Abstract

The development of an antibody in people with hemophilia to products used in the treatment and prevention of bleeding, also referred to as an inhibitor, is the most serious complication of hemophilia care today. CDC, together with healthcare providers, consumer organizations, hemophilia organizations, and federal partners, has developed a public health agenda to prevent the development of inhibitors. This paper describes a public health approach that combines a national surveillance program with epidemiologic, laboratory, and prevention research to address knowledge gaps in rates and risk factors for inhibitor development, and in knowledge and behaviors of patients and providers, in addition to screening and treatment practices.

Introduction

The primary congenital bleeding disorders are hemophilia A and B, which are deficiencies in a protein (factor) that is necessary for normal blood clotting, and affect approximately 1 in 10,000 and 1 in 35,000 male Americans, respectively.[1] As many as one third of patients with severe hemophilia A will develop an antibody (i.e., *inhibitor*) to the factor replacement products that are infused intravenously to stop or prevent a bleeding episode.[2] Most inhibitors develop during the first few infusions with factor, which, among those with severe hemophilia, usually occur before age 2 years although all patients are at risk of developing an inhibitor.[3] An inhibitor neutralizes a treatment product's ability to control bleeding.

The healthcare costs associated with inhibitors are staggering. Patients with inhibitors are twice as likely to be hospitalized for a bleeding complication.[4] In addition, compared with the cost of care for patients without an inhibitor, the cost of care for those with an inhibitor

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who have a bleeding complication is four to five times greater and, in some cases, may exceed a million dollars annually.[5,6]

Improvements in clotting factor safety and efficacy over the past several decades, along with the widespread use of prophylaxis, have greatly decreased hemophilia-related morbidity and mortality. Prophylactic therapy (infusion of factor products to prevent bleeding episodes) is considered the standard of care for patients who do not have an inhibitor, and primary prophylaxis (i.e., therapy started before the second clinically evident large joint bleed and age 3 years) has been shown to decrease frequency of hemarthroses and prevent long-term joint damage.[7]

Although these advancements in care and treatment have, in many cases, led to a nearly bleed-free life, this is not true for patients with an inhibitor, who continue to have bleeding episodes that require frequent and costly treatment and often take longer to resolve and, therefore, have a greater potential effect on quality of life owing to missed days at school or work.

Patients with an inhibitor have significant care management considerations beyond those without an inhibitor. Because there are fewer factor replacement choices for patients with an inhibitor, medical management often is more complex. Treatment for the inhibitor can include use of more expensive inhibitor-bypassing drugs or immune tolerance induction (ITI) therapy, which requires frequent infusion of large doses of factor products. Venous access can become difficult and may require the use of venous access devices, arteriovenous fistulas, or both.

Surgical intervention often is more complex, given limited access to surgeons with experience operating on patients with an inhibitor. The increased cost creates an additional financial burden, as well as difficulty navigating insurance options and management. Even with treatment, patients with an inhibitor are significantly more likely to die from bleeding complications than those without an inhibitor.[8]

The purpose of this paper is to describe a public health approach that combines a national surveillance program with epidemiologic, laboratory, and prevention research to address knowledge gaps in the epidemiology and prevention of inhibitors in the U.S.

Causes of Inhibitors

Inhibitors are antibodies developed by the body's immune system in response to an infused replacement factor. Although genetic factors, such as the *F8* or *F9* gene mutation and polymorphisms within certain immune system genes, are known to influence the risk of developing an inhibitor,[9] environmental and treatment factors also can play a role.

For example, a cohort study[10] of previously untreated patients with hemophilia followed for the first 75 exposure days at 26 European treatment centers observed that periods of "intense treatments" (in which factor replacement was given for 5 or more contiguous days) were more likely to lead to inhibitor development. Further study of other treatment-related risk

factors such as product switching, continuous factor infusion, infections, and surgical or non-surgical procedures is necessary for development of better prevention strategies.

National Surveillance for Inhibitors

Hemophilia is a rare condition, affecting an estimated 22,000 male Americans. Although as many as one third of these patients might develop an inhibitor at some point, in any given year the number of new inhibitor cases is relatively small. Surveillance from the United Kingdom has found an overall incidence rate of inhibitor development among patients with severe hemophilia of 10.92 per 1,000 person-years.[11]

Therefore, monitoring of a large proportion of the U.S. population with hemophilia will be necessary to obtain accurate measures of incidence and prevalence, effectively monitor trends in occurrence rates over time, and assess risk factors for developing inhibitors. Monitoring large numbers of patients also will be required to determine whether apparent clusters of inhibitor cases represent an actual increase that might be caused by something preventable or are just due to chance. National surveillance with centralized testing for inhibitors can provide other advantages over individual local, regional, or multisite efforts, including standardized inhibitor screening tests administered on a regular basis, confirmation of local inhibitor testing results, and consistent monitoring and reporting of national inhibitor occurrence rates.

The Role of the U.S. Hemophilia Treatment Center Network

In the early 1970s, the development of clotting factor concentrates that were effective at stopping bleeding episodes and could be administered to patients outside of a hospital setting led the U.S. Government to establish a network of specialized hemophilia treatment centers (HTCs) in 1975 in order to provide multidisciplinary care to patients with hemophilia.[12] A population-based study[1] in the 1990s showed that about 70% of the U.S. population with hemophilia was receiving care in these centers. Furthermore, the study showed that rates of both mortality and hospitalization for bleeding complications were lower among those receiving care in the HTCs than among those receiving care elsewhere.[4,13]

In 1998, CDC established a surveillance system in the HTCs to monitor care practices and patient outcomes, including monitoring for product-transmitted infections.[14,15] Although the system was not specifically designed to study inhibitors, analysis of data from the surveillance system revealed that less than one half of patients were being screened regularly for inhibitors (JMS, unpublished observations, 2013).

Because the patient and provider communities have identified inhibitors as an issue of concern, CDC has begun national surveillance for inhibitors in the HTCs, with the CDC Division of Blood Disorders laboratory providing prospective inhibitor testing using methods developed as part of a research study supported by public and private funding[3,16] and the HTCs providing clinical expertise and data to characterize risk factors for inhibitor development.

Identification of risk factors for the development of inhibitors is necessary to avoid practices that can increase the likelihood of inhibitor development. Anecdotal reports and a single-institution case series have suggested that early prophylaxis begun in the first year of life and prior to the first joint bleed lowers the risk of inhibitor development.[17] Avoidance of treatment with factor VIII (FVIII) replacement therapy coincident with vaccine administration has been recommended by some in order to avoid a theoretic “danger signal” that might trigger an immune response after FVIII exposure.[17,18]

Although most inhibitors appear before the first 50 treatments with factor replacement (exposure days), clinical trials that enrolled patients with more than 150 exposure days prior to trial entry revealed that new inhibitors might develop well beyond the first 50 exposure days.[19] The calculated risk of inhibitor formation after 150 exposure days, based on a systematic review of 33 different studies, was estimated to be approximately 3 per 1,000 person-years.[19]

Rarely, new inhibitors have been linked to specific factor-replacement products, and this discovery has led to a better appreciation of possible alterations of the FVIII protein that render it more immunogenic.[20] The role of specific treatment products is very difficult to determine even when utilizing meta-analyses, because the studies use different patient populations and frequencies of inhibitor testing. Better precision from prospective monitoring will help to establish a “standard risk,” to which the risk of new products undergoing evaluation for safety in clinical trials can be compared. Many patients are reluctant to switch treatment products because of a realistic fear that a new inhibitor might emerge; however, better risk stratification will help to inform their decisions.

Inhibitors that result from a very strong immune response, called high-titer inhibitors, necessitate a change in treatment product and regimen, whereas low-titer inhibitors can be overcome by increasing the dose of FVIII. In some cases, low-titer inhibitors can be transient and disappear without change in treatment. Cross-sectional studies will not detect the majority of the transient inhibitors, and even if they are detected, it is unlikely that such an inhibitor would be correctly categorized as self-resolving.

Patients with mild hemophilia have a lower risk of inhibitor formation. However, because their exposures to treatment products more frequently are associated with surgeries, an unrecognized inhibitor could have catastrophic outcomes. Once factor replacement treatment is discontinued, inhibitors might become low titer or not detectable, which could lead to an underestimation of inhibitors among patients with mild hemophilia in cross-sectional studies or in prospective studies with very short follow-up periods. Therefore, long-term prospective monitoring can better assess the occurrence and clinical significance of inhibitors among those with mild hemophilia.

A component of the national inhibitor surveillance will be the retrospective data collection on genetic and environmental treatment–related risk factors in the previous 4-month period at the time of new inhibitor identification. Although retrospective data have limitations, collecting these data (including factor infusion logs) from all patients prospectively is not feasible given the high costs of HTC staff time for the follow-up required to ensure patient

adherence to reporting.[3] A partnership combining the clinical expertise of the HTCs and the epidemiologic and laboratory skills of CDC is ideal for mounting an effective national surveillance program of and collecting data on treatment-related risk factors for a large American cohort to identify which treatment practices are associated with a greater likelihood of inhibitor development and, therefore, should be avoided.

The Role of a Central Laboratory

Inhibitors occurring among patients are measured by their ability to inhibit factor activity in vitro. Measurement of hemophilic inhibitors in the U.S. was standardized in 1975 at a meeting in Bethesda MD, which produced a method bearing the name of the conference site.[21] The Bethesda assay method has persisted virtually unchanged in the majority of laboratories in the U.S. Modifications to the method—called the Nijmegen–Bethesda assay and recommended by the International Society on Thrombosis and Haemostasis—were introduced in Europe in 1995[22,23] but have not been adopted widely in the U.S.[24]

The United Kingdom and European Union inhibitor surveillance programs rely on test results reported from local laboratories; however, proficiency testing has shown a high degree of inter-laboratory variability in results of inhibitor tests in Europe,[25] the United Kingdom,[26] and the U.S.,[24] which could lead to inconsistencies in the collected data. Regulatory bodies have recommended either centralized testing for inhibitors or quality control systems to monitor local laboratories as part of national registries,[27] and CDC has concluded that centralized testing is needed initially to provide the degree of standardization required to accurately assess the prevalence and incidence of inhibitors in the U.S. hemophilia population.[3]

The performance of large numbers of tests by a central laboratory, as piloted by CDC,[3] will result in economies of scale, enhanced quality control, and the availability of large data sets for analysis. Reagents, such as buffered normal pooled plasma, can be prepared or purchased in bulk. Quality control testing materials, which are not available commercially, can be prepared and used consistently. Analysis of large data sets has led to the recognition of systematic testing problems and development of improvements in methods used for inhibitor measurement.[16,28]

Validation of a modification to the Nijmegen–Bethesda assay for removing infused FVIII prior to inhibitor measurement has facilitated surveillance by allowing patients on prophylaxis and those recently treated to be tested without refraining from factor use.[16] The ability to test for an inhibitor in the presence of FVIII has the potential to facilitate more complete monitoring of the hemophilia population for inhibitors. Study of large numbers of patients with a single method has allowed development of a more accurate definition of a positive inhibitor result and the addition of more sensitive and specific assays to confirm questionable results.[28]

Although standardized methods are crucial for surveillance purposes, they also are important for clinical care to allow early detection of inhibitors and monitoring of therapy, such as ITI. Technical advances in inhibitor measurement developed at CDC will be disseminated to local laboratories used by providers of care to patients with hemophilia. This process will be

monitored by verification of local laboratory testing results by repeat testing of samples at the CDC laboratory. It is expected that dissemination of the standardized testing methods to local laboratories will increase the accuracy and efficiency of case-finding activities in the future and will facilitate the transition of the role of the CDC laboratory from the performance of centralized testing to serving as a reference laboratory for monitoring and quality control.

The Contribution of Public Health Research to Inhibitor Prevention

The public health goal of inhibitor surveillance and research is to reduce the incidence of inhibitors. In the U.S., surveillance with centralized testing will determine the magnitude of this adverse event through measurement of the incidence and prevalence of inhibitor development among patients. Inhibitor research is needed to characterize inhibitor testing among current providers, describe inhibitor characteristics and clinical outcomes, identify key genetic and environmental risk factors, and determine patient health information needs regarding inhibitors.

Public health research is needed in the U.S. to identify standardized, evidence-based intervals for inhibitor testing. Early identification of inhibitors has been correlated with increased treatment success and decreased duration of inhibitor treatment.[29] Studies are needed to characterize provider testing practices and determine the ways in which knowledge and awareness of inhibitors can influence testing practices. Assessment of the barriers and facilitators to routine inhibitor screening will inform the development of interventions.

Public health laboratory research is needed to (1) characterize inhibitor titer levels over time; (2) investigate inhibitor characteristics, such as reactions with specific products, epitope specificity, and kinetics; and (3) correlate these characteristics with clinical outcomes, including inhibitor transience and response to ITI therapy. Data from these studies will be used to generate evidence-based, standardized definitions of both transient and clinically significant inhibitors that, in turn, will allow clinicians to provide more rapid and appropriate treatment.

Epidemiologic studies are needed to further elucidate the risks and protective factors for inhibitor development. Surveillance efforts will facilitate research efforts by providing access to the necessary large sample sizes required to examine patient immune response variations, product exposure risks, and potential protective factors for inhibitor development. The results of studies of the interactions between these genetic and environmental risk factors then can be used to develop patient-specific risk algorithms for inhibitor development.

Prevention research is needed to assess the health information needs of patients with and at risk for inhibitors and to develop interventions. Despite the fact that inhibitors have been identified as a priority issue by the hemophilia community, no studies have examined patient knowledge and awareness of inhibitors; experiences with testing, diagnosis, and treatment; and barriers and facilitators to testing and treatment. Such research is needed to develop, implement, and evaluate interventions to address these issues. Gaps in knowledge among

patients can negatively influence participation in needed research studies in the short term and can decrease the effectiveness of future inhibitor reduction strategies in the long term.

Finally, research is needed to assess the full economic effect of inhibitor development in the U.S. Current research has demonstrated that the cost to treat a single inhibitor patient can exceed 1 million dollars per year.[5,6] However, little research has been done in the U.S. to document the direct inpatient, direct outpatient, and indirect costs associated with care for patients with inhibitors. The results of such research will be needed to evaluate the cost-effectiveness of future interventions and inform policy decisions regarding resource allocation.

Conclusions

Inhibitor development is currently one of the most important causes of morbidity for patients with hemophilia in the U.S. Prevention will require a comprehensive public health approach that includes not only surveillance, but epidemiologic, laboratory, and prevention research. Partnerships with the HTCs, consumer organizations, hemophilia organizations, and federal partners are vital to accomplishing CDC's public health goal of preventing inhibitor development.

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